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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,091	05/06/2005	Juha-Matti Savola	TUR-168	2654

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
09/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,091	SAVOLA ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments and Arguments

1. Applicant's arguments filed 6/25/09 have been fully considered but they are not deemed to be persuasive.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 23 and 25-33 are pending in this office action.

4. The objection to claim 23 is withdrawn due to the claim amendment.

5. The rejection of claims 23 and 26-33 under 35 U.S.C. 112 as failing to comply with the written description requirement is withdrawn due to the claim amendment.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23, 25-29 and 31-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huupponen (1995) in view of Karjalainen et al., (US 5,498,623) for the reasons made of record in Paper No. 20090506 and as follows.

Applicant argues that the claimed method requires a formulation containing fipamezole to be administered to a patient by oromucosal administration, wherein the administration is via the oral mucosa of the patient. Applicant further states that they discovered that the problem of QTc prolongation is avoided when fimpamezole is oromucosally administered.

Applicant also argues that "[b]ased on the teachings of Huupponen et al., the ordinarily skilled artisan would have expected that oromucosal administration of fipamezole would analogously increase its bioavailability, increasing circulating levels of

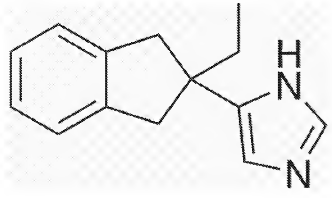
fipamezole as compared to levels achieved by oral administration of an equal fipamezole dose" and "[a]s a consequence, the person of ordinary skill would have expected oromucosal administration of fipamezole to increase fipamezole's dose-dependent side effect and not have expected oromucosal administration of fipamezole to increase fipamezole's dose-dependent side effect".

Applicant also argues that "Karjalainen discloses fipamezole, its preparation and use as an antagonist to α2-adrenoceptors" that may be administered orally. Applicant further argues that "the only difference between the claimed method and Karjalainen et al. is the mode of administration. Accordingly, the question of whether the claimed method produces an unexpected result is properly considered against Karjalainen et al. rather than Huupponen et al., which is directed to a different compound".

It is further argued that the cited prior art fail to disclose or suggest that oromucosal administration of fipamezole will avoid QTc prolongation.

In response it should be noted that this rejection is a rejection under 35 USC 103 and not a rejection under 35 USC102. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *See In re Keller*, 642 F 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck &Co.*, 800 F.2d 1091, 231 USPQ (Fed. Cir. 1986).

Nonetheless Huupponen teaches atepamezole (i.e.,



) that has the same core, same class and functionally and structurally similar to the claimed compound fimpamezole. Atepamezole is a homolog of fipamezole and shares the same characteristics with fimpamezole. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious. In re Hass, 60 USPQ 544 (CCPA 1944); In re Henze, 85 USPQ 261 (CCPA 1950). Also recognized classes of chemical compounds mean that there is an expectation in the art that members of the same class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other with the expectation that the same intended result would be achieved.

Further Huupponen specifically teach the compound is administered oral mucosally via spraying. Karjalainen is introduced for its teaching of compounds that encompasses Huupponen's compound that includes the recited compound (same family). Therefore one of ordinary skill in the art would have reasonably substituted Huupponen's atepamezole with Karjalainen's fipamezole and formulated a spray for oral mucosal administration because it is taught by Huupponen that compounds of the same

core structure that are α_2 adrenergic receptor antagonist (a species of the generic formula I in its acid salt) may be administered in the form of a spray oromucosally (see page 506, abstract) As to the assertion that "whether the claimed method is properly considered against Karjalainen rather than Huupponen which is directed to a different compound" it should be noted that the teachings of Karjalainen encompass compounds of Huupponen, therefore one of ordinary skill in the art would be motivated to substitute Huupponen's compound with Karjalainen's compound and expect the same result. Therefore Applicant's argument that with Huupponen "...the ordinarily skilled artisan would have expected that oromucosal administration of fipamezole would analogously increase its bioavailability, increasing circulating levels of fipamezole as compared to levels achieved by oral administration of an equal fipamezole dose" and "[a]s a consequence, the person of ordinary skill would have expected oromucosal administration of fipamezole to increase fipamezole's dose-dependent side effect and not have expected oromucosal administration of fipamezole to increase fipamezole's dose-dependent side effect" is not persuasive. The therapeutic activity that is relied upon by Applicant is a functional characteristic that is inherently or intrinsically present upon the administration of the drug. The argument that the cited prior art fails to disclose or suggest that oromucosal administration of fipamezole will avoid QTc prolongation is found not persuasive because Huupponen specifically teach that in their study plasma, and heart rate were practically unchanged. Therefore if the plasma concentration is unchanged, there will be no QTc prolongation.

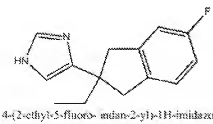
The argument that QTc prolongation is unpredictable is also found not persuasive, and the article submitted on 2/17/09 (the FDA's Guidance for Industry S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (FDA October 2005)), is not considered relevant to the claimed invention because the information therein was published 7 years after the priority date of the claimed invention.

Applicant's arguments have been fully considered but they are not persuasive as discussed above and already made of record.

In Summary:

Huupponen teaches an α_2 adrenergic receptor antagonist (a species of the generic formula I in its acid salt) that is administered in the form of a spray oromucosally (see page 506, abstract; and Introduction as required by instant claim 23 in part, dissolved in ethanol and water (i.e., solvent; as required by instant claims 26- 27 in the form of spray as required by instant claims 31 and 32.

However Huupponen fails to teach the exact compound

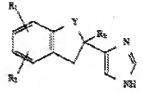


4-(2-ethyl-5-fluoro- indan-2-yl)-1H-imidazole

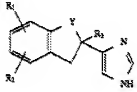
as required by instant claims 23 and 35 in part, and also fails to teach the formulation consists of a preservative (i.e., methyl

parahydroxybenzoate) and the flavoring agent aspartame and black currant as in claims 29-30 and 33, and also the addition of a preservative and a flavoring agent to the formulation (as required by instant claims 26, 28, 29).

Karjalainen et al. teach the claimed compound as in current claim

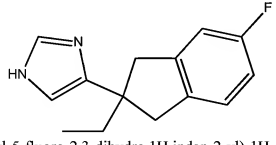


23 which is identical to the claimed compound of the claimed

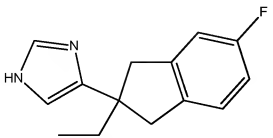


invention , wherein Y is CH_2 or CO, R_1 is a halogen or hydroxyl, R_2 is hydrogen or halogen and R_3 is hydrogen or lower alkyl-methyl (see abstract in a pharmaceutical composition administered orally (see abstract and also see col. 4, lines 62-63). Reasonably to have an oromucosal administration.

With regards to claim 25 Karjalainen teaches (see abstract



also) 4-(2-ethyl-5-fluoro-2,3-dihydro 1H indan-2-yl)-1H-imidazole is the same as



4-(2-ethyl-5-fluoro- indan-2-yl)-1H-imidazole or its acid salts (i.e., hydrochloride salt of (see col. 7, lines 48-50).

Karjalainen et al. also teach that the solvent is ethanol (as required by instant claim 27; see col. 7, lines 63-64).

However Karjalainen fails to teach specifically oromucosal administration and the addition of a preservative and a flavoring agent to the formulation (as required by instant claims 26, 28, 29, 31-33). Even though Karjalainen failed to teach the addition of flavoring and or preservative it is however taught that "choosing auxiliary ingredients for the formulation is routine to the ordinary skill in the art and is evident that suitable solvents, colors etc are used in a normal way".

That being said it would have been obvious to one of ordinary skill in the art to add flavoring (i.e., sweetener) to the spray formulation for the improvement of the taste since the patient would preferably and willingly administer the sweet tasting spray versus a bitter tasting spay that is directly placed in the oromucosal cavity.

It would have been obvious to add a preservative to any drug formulation for the prolongation of shelf life. These are routine procedures employed in the art of formulation as indicated above by Karjalainen. One of ordinary skill in the art would have substituted Huupponen compound with Karjalainen since both compounds are α_2

adrenergic receptor antagonists and one would reasonably expect the formulation for oromucosal to be successful.

7. Claims 23, 25-30 and 31-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huupponen (1995) and Karjalainen et al., (US 5,498,623) in view of De Prost (US 6,413,988) for the reasons made of record in Paper No. 20090506 and as follows.

Huupponen and Karjalainen are applied here as above. However both Huupponen and Karjalainen fail to teach the addition of a preservative and a flavoring agent to the formulation (as required by instant claims 26, 28, 29, 30 and 33).

De Prost teaches an aqueous pharmaceutical solution of prucalopride employed as a spray for oral administration that comprises a preservative for inhibiting the growth of micro-organism (see col. 2, lines 30-45 and col. 3, lines 14-16) wherein the preservative is a parahydroxybenzoate salt (see col. 4, lines 58-67) and the flavor is aspartame and black currant (see col. 2, lines 46-47 and col. 3, lines 1-4).

However De Prost fails to teach the claimed compound femiprazole and oromucosal administration.

It would have been obvious to one of ordinary skill in the art to have employed the teaching of De Prost of a spray formulation with a preservative and a sweetener with the teaching set forth by Huupponen and Karjalainen because as taught by De Prost these are added to liquid oral formulations such as sprays to inhibit microbial growth and to affect the taste by masking the bitter tasting effect. As known to one of ordinary

skill in the art, aspartame is an intense sweetener and therefore capable of masking taste and black currant would give a fruity taste to the formulation and may enhance the sweetening capability of aspartame when combined.

Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

8. No claim is allowed

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. V. G./
Examiner, Art Unit 1618, 9/1/09

/Robert C. Hayes/
Primary Examiner, Art Unit 1649